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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,714	05/08/2002	Audrey Goddard	P3230R1C001-168	8614

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,714	GODDARD ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,11-14 and 16-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-6, 11-14 and 16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/16/05,7/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Response, Information Disclosure Statements, and Amendments, submitted 16 may 2005 and 5 July 2005, have been entered. Claims 4, 5, 6 and 14 are amended. Claims 1-3 and 7-10 are cancelled. Claims 21-31 are new.

Claims 4-6, 11-14 and 16-31 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

Continuity

The objection to the Specification for not complying with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119, is *withdrawn.* The filing date of the PCT Application (24 August 2000) is considered as the priority date.

Maintained/New Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 4-6, 11-14 and 16-31 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pages 4-10 of the previous Office Action (17 February 2005). Claims 4-6, 11-14 and 16-31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (17 February 2005), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (*Remarks*, 16 May 2005, page 7 and throughout) that the data presented in the instant Specification are enabling for the polynucleotide of SEQ ID NO: 85. They argue that the PRO1302 nucleic acid is a diagnostic marker for *normal esophagus*, and point to the results of the assay which showed transcription of the PRO1302 DNA in one normal versus cancerous tissue. Applicants point out that the PRO1302 data of Example 18 refers to *transcription data*, not DNA amplification data (Response, page 11 and throughout).

Applicant's arguments (20 April 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an indeterminate increase in mRNA in one normal tissue (see Example 18, Specification). However, there is no evidence regarding whether or not PRO1302 polypeptide levels are also increased in *normal esophagus*

tissue versus *esophageal* tumor. Furthermore, as discussed in the previous Office Action (17 February 2005, pages 4 and 5), what is often seen is a *lack* of correlation between mRNA levels and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Given the small increase in transcription of PRO1302 DNA, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in message would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1302 message supports a role for the peptide in detecting or treating cancerous tissue; such a role has not been suggested by the instant disclosure. The requirement for further research makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further

experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1302 peptide has utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

There is no evidentiary support that PRO1302 is involved in the etiology of cancer in the one sample disclosed in the instant Application. Furthermore, as noted above, the *decrease* in PRO1302 message, and in only one tissue, points away from its role in a disease. At any rate, one result is too little data to make a conclusion about PRO1302 and cancer. It should be noted that the *specific* function of the PRO1302 polypeptide has not been disclosed by Applicants or by recent research. Although transductional and structural information are not absolutely necessary when applying for a patent on a new protein, it would be very useful to have such information for the PRO1302 polypeptide, since there is only one positive data point in the transcription assay, and that is in one normal tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

Applicants discuss (Response, 16 May 2005, page 9 and throughout) points from case law in reference to the utility rejection, most of which the examiner agrees with. However, the fact patterns of the cases cited have little connection with utility/enablement as applied to the instant Application. Whatever the asserted specific utility might be - diagnosis of cancer, for example- it is **not** "more likely than not" (In re Oetiker, 1992, 977 F2d 1443, 1445, 24 USPQ2d) or true "to a reasonable probability" (Fujikawa v. Wattanasin, 1996, 93 F3d 1559, 39 USPQ2d 1895) since the increase in message was found in only one normal tissue sample.

Applicants discuss the Declarations submitted previously under 35 USC §1.132 to explain how data were gathered, etc. For example, the Declaration from Dr. Grimaldi explains that data from several of the same tissues are pooled. This results in a difference of expression between the positive and negative tissue of 2-fold.

Applicant's arguments (16 May 2005) have been fully considered but are not found to be persuasive for the following reasons:

As discussed in the previous Office Action (17 February 2005), a 2-fold increase is not large and may be less likely to indicate disease (Hu, et al, 2003, Journal of Proteome Research 2:405-412), or may be sufficient (Applicant's Response, page 14). However, the type or magnitude of increase is not at issue in this case. All that is known about the PRO1302 peptide is that it is increased in one normal tissue. It cannot be determined what the function of the protein is in the tissue; certainly the tissue provides no clues. It is hard to conceive of a specific and substantial utility for a protein for which so little data or information is given. For example, why were other tissues not tested, as was the case for other PRO polypeptides? What might be

the connection between one normal tissue and one cancerous tissue that would provide clues to the protein's function?

Applicants do not know the function of the PRO1302 polypeptide. For this reason, detecting the PRO1302 mRNA or polypeptide has no specific function, since it is not useful to detect a protein for which a function has not yet been identified, and additionally might only be overexpressed in one normal tissue. Since the asserted utility for the PRO1302 polypeptide is not in currently available form, the asserted utility is not substantial.

35 USC § 112, first paragraph – Written Description.

Claims 4-6, 11-14 and 16-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 10-11 of the previous Office Action (17 February 2005). Briefly, the Applicants were not in possession of all or a significant number of polynucleotides that have 95% homology to SEQ ID NO: 85, while retaining the function of SEQ ID NO: 85.

Applicants discuss the legal standards applied when evaluating Written Description, including the requirement that written description depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (pages 29-31, 16 May 2005). The examiner takes no issue with the discussion of general requirements for evaluating

Written Description in this case. However, Applicants have not described or shown possession of all polynucleotides 95% homologous to SEQ ID NO: 85, *that are functionally equivalent to SEQ ID NO: 85.* Nor have Applicants described a representative number of species that have 95% homology to SEQ ID NO: 85, such that it is clear that they were in possession of a genus of polynucleotides functionally similar to SEQ ID NO: 85. Applicants screened for one PRO1302 sequence, and used that one sequence in several expression and detection protocols (see Example 130 and Table 8). Applicants have not made sequences different from SEQ ID NO: 85 or 86. Nor have Applicants discussed possible post-translational modifications in this PRO nucleotide.

As discussed in the previous Office Action (17 May 2005) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1302 polynucleotides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein said nucleic acid is more highly expressed in normal esophagus..." (Amended claims, 16 May 2005), is not adequate to describe the PRO1302 polynucleotides that have 95% homology to the PRO1302 polynucleotide, since there was no reduction to practice to support the amended claims. Applicants made no variant polynucleotides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
20 July 2005

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